Remarks

Applicants request reconsideration of the application and entry of the foregoing amendments under the provisions of 37 C.F.R. 1.115. Applicants respectfully assert the amendments submitted herewith obviate the rejection, thereby placing this application in condition for allowance, or, alternatively, in better condition for appeal.

Three documents are submitted for consideration. Proprietary and trade secret information has been redacted where appropriate per MPEP §724.

Claims 35 and 65-66 are pending. New claims 67-68 further distinguish the claimed invention over the cited art. New claims 67-68 address a combination regimen in which PTH(1-34) is co-administered with calcium and vitamin D (claim 67), or vitamin D only (claim 68). Support for these claims appears at pages 4 and 47 of the specification. Applicants submit no new matter has been added and request entry of the amendment.

Rejection Under 35 U.S.C. Section 102(b)

Claims 35, 65 and 66 stand finally rejected under 35 U.S.C. § 102(b) as being anticipated by Neer, et al. (Neer). Applicants respectfully traverse the rejection as it is applied to these claim and newly added claims 67-68. Neer does not anticipate the present claims, at least for the reasons set forth below.

Summary of Argument

Applicants discovered that PTH(1-34) administered daily at a 20 microgram dose reduces the risk of fracture in both vertebral and non-vertebral bone in human subjects. The rejection alleges that Neer et al. ("Neer") anticipates the claimed invention. Neer teaches administration of 100-700 units of human PTH(1-34) to osteoporosis patients. Neer does not teach the corresponding microgram dosage, nor the specific activity for determining such. A skilled artisan cannot compare "units" of activity directly with micrograms without knowing the specific activity conversion relationship.

Anticipation requires comparison of a single prior art reference to the claimed invention. Anticipation cannot rest on combining references. The present rejection combined Neer with other prior art references to import a specific activity value. In so doing, it exceeded the narrow exception that allows combining references in an anticipation only to "explain" the meaning of the primary reference.

Neer Fails To Disclose The Specific Activity for PTH(1-34)

Anticipation requires that a comparison be made between a single prior art reference and the claimed invention. An anticipatory reference must teach each element of the claimed invention, expressly or inherently. In the present case, a skilled artisan cannot directly compare Neer's disclosure with Applicants' claimed invention. Neer does not provide the needed "key" for converting "units" to micrograms - the specific activity value.

Nor does Neer provide for an alternative approach - experimental determination. Neer teaches that units of activity were measured in the chick hypercalcemic assay (Col 5). The passage further states that "units are defined in terms of the International Reference Preparation of hPTHF 1-34" (Col 5). Dr. Meiklejohn submitted a declaration that he does not believe there currently exists, or ever has existed, an appropriate International Reference Standard for human PTH(1-34). Dr. Meiklejohn further declared that he is not aware of the existence of the specified "International Reference Preparation of human PTH(1-34)." Without public access to Neer's reference standard, Dr. Griffiths declared that one could not determine the specific microgram equivalent of Neer's unit dosage, nor compare Neer to other data or samples.

Meaningful comparison of Neer's units dosage with other PTH(1-34) samples requires measurement in the *same* assay, against the *same* reference standard. Absence of the specific PTH(1-34) reference standard stipulated by Neer means there is *no way* to unambiguously compare a PTH(1-34) sample with the "units" disclosed by Neer.

Applicants submitted evidence showing that the activity of PTH is quite sensitive to the particular assay used and the particular standard used for calibration (See prior Griffiths declaration). The Examiner has not provided evidence to rebut Applicants' evidence. To the contrary, the Examiner is on the record as having recognized the ambiguity and uncertainty in trying to compare microgram amounts of PTH with activity. In the First Office Action (Paper 9, p. 4) he states, "the amount (ug) of a parathyroid hormone is [sic] depends upon the purity, activity, and size of the hormone or its active fragment."

The Law on Anticipation Prohibits Combining Neer With External References to Provide the Specific Activity for Neer's PTH(1-34)

In the Office Action dated November 12, 2002, the rejection proposed a specific activity of 25 micrograms = 400 units (i.e. 16 U/ug).[1] In the Final Action, the rejection proposed a conversion of 40 micrograms = 500 units (i.e. 12.5 U/ug). Finally, the rejection calculated an "average" specific activity based on twelve prior art references disclosed by Applicants in Paper 10. These actions import substantive information into Neer that was not already there, and in so doing violate the rule against combining references to show anticipation.

It is hornbook law that anticipation requires a showing of each element, expressly or inherently, in a single reference. *Studiengesellschaft Kohle, m.b.H. v. Dart Industries*, 726 F.2d 724,726-27 (Fed. Cir. 1984). According to the MPEP, an examiner may refer to extra references, or extrinsic evidence, in deciding the issue of anticipation to *explain* but *not expand* the meaning of a primary reference. MPEP 2131.01 (B).

Reliance on extra references under the MPEP 2131.01 Section (B) exception is permitted to "explain but *not expand the meaning of terms and phrases*" used in an allegedly

[1] November 12, 2002 Office Action, paper no. 9, page 5. It appears that this conversion factor was taken from Lindsay, et al. (IDS code CB); Lindsay, et al (IDS code CD) and Lane, et al. (IDS code CE)

anticipatory reference. An examiner may cite extrinsic references but only for the narrow purpose of showing what is *de facto* present in a primary reference. "Explanation" contemplates revealing what exists, not adding to what exists, and not speculating about what *might* exist.

To illustrate this narrow exception, the MPEP cites *In re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed Cir 1991). In *Baxter*, the court upheld the Examiner's reliance on extrinsic references to show that "commercial two bag blood containers" would necessarily teach a bag that contained the plasticizer "DEHP" as a component. At the time of the application, DEHP was *known* to be a component in "commercial two bag blood containers." Reference to secondary sources in this case did nothing more than reveal what was already present in the primary reference. Thus, reliance on more than a single reference is limited to explaining what a particular term or phrase necessarily and unequivocally conveys to a skilled artisan. The law does not permit importation of information that is not already there.

In another case on point, the Federal Circuit held it unacceptable to combine a primary reference with additional references in reliance on their "very specific teaching, not for any light they shed on what Fischer would have meant to those skilled in the art . . . ." *Studiengesellschaft Kohle*, 220 USPQ 841 (Fed. Cir. 1984).

The prohibition against importing specific teachings into a primary reference in an anticipation rejection is further amplified in *University of California v. Eli Lilly and Company*. In that case, Lilly successfully argued that claims to a plasmid vector encoding a cDNA for human insulin were anticipated by a prior art reference that taught a plasmid encoding a fusion protein encoding human proinsulin. *Regents of University of California v. Eli Lilly and Company*, 39 USPQ2d 1225 (S.D. Ind. 1995). The human insulin amino acid sequence was not taught in the primary reference. Nevertheless, the court allowed Lilly to combine the primary reference with a secondary reference to show that the amino acid sequence of human insulin was known to the skilled artisan at the time of UC's filing. The court stated that

extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the [primary] reference, and that it would be so recognized by persons of ordinary skill." (citing *Continental Can Co. v. Monsanto*, 848 F.2d 1264, 1268 (Fed. Cir. 1991)).

The rejection in the present case violates the prohibition against relying on multiple references to find anticipation. The rejection rests on importing specific activity values for PTH(1-34) from the prior art to convert Neer's "units" dosage to micrograms. Unlike the *Baxter* case, here there is no credible basis to argue that the prior art teaches or in any way relates to *Neer's* specific activity. None of the references relied upon in the rejection even intimates, let alone stipulates, that the specific activity values taught in the reference applies to Neer. In fact, none of the references relied on even mentions the Neer reference. As such, there is no basis to contend that the specific activity values imported from the prior art reveal *Neer's* specific activity, or "explain" Neer's specific activity.

The question is not whether *any* specific activity value could be conjured up, or imported from the prior art to interpret Neer. The issue is whether a skilled artisan could ascertain within the four corners of Neer, or by reference to extrinsic evidence, basis for making the specific conversion of *Neer's* "units" dosage to the corresponding microgram quantity. Neer does not disclose the particular specific activity by which to make this conversion.

The present rejection exceeds the narrow "explanation exception" by importing information into Neer that was not already there. Unlike *Baxter*, in which the allowed secondary references taught what was in fact present in the primary reference, albeit unstated, here the secondary references relied upon do not teach, nor do they purport to teach, the critical specific activity information missing from Neer. The rejection rests not upon *explaining* what Neer taught to the public, but upon *speculating* about what Neer hypothetically *could* have taught. The rejection relies on secondary references that in fact *supplement* Neer with

information that is not present in Neer. This action exceeds the permissible bounds for an anticipation rejection.

In this light, the *Scripps* decision is relevant. *Scripps Clinic v. Genentech*, 18 USPQ2d 1001 (Fed. Cir. 1991). According to Scripps:

> It is sometimes appropriate to consider extrinsic evidence to explain the disclosure of a reference. Such factual elaboration is *necessarily of limited scope . . .*, for a finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. . . .*If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not Section 102 anticipation, but Section 103 obviousness.* (emphasis added)

Applicants have provided unrebutted evidence that determination of Neer's specific activity is not possible based on Neer's disclosure. Moreover, reliance on secondary references to import a specific activity exceeds the permissible limitations of an anticipation rejection. Accordingly, Neer cannot be said to anticipate the present invention.

Anticipation Cannot be Based on Mere Possibility

The standard for anticipation is quite high. The law requires that a single prior art reference expressly or inherently teach the claimed invention. Uncertainty or ambiguity as to what is taught by an allegedly anticipatory reference eviscerates any basis for an anticipation argument.

In *Ex parte Standish*, the Board of Patent Appeals overturned a rejection under Section 102 based on conjecture as to what was taught by an allegedly anticipatory reference. In *Standish*, the Examiner rejected claims to an audible fishing lure for anticipation, principally based on the examiner's interpretation that a figure in a prior art reference may have disclosed a key element of the claimed invention. The Board held, "anticipation of a claimed product

cannot be predicated on mere conjecture as to the characteristics of a prior art product." *Ex parte Standish*, 10 USPQ2d 1454 (BPAI 1988).

In *Motorola v. ITC*, the court overturned a judgment of invalidity based on anticipation stating, "For a prior art reference to anticipate a claim, the reference must disclose each and every element of the claim *with sufficient clarity to prove its existence in the prior art*. (emphasis added) *Motorola v. ITC*, 43 USPQ2d 1481 (Fed. Cir. 1997).

The *Motorola* court further stated, "Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." See also *In re Spada* ("The prior art reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"), 15 USPQ2d 1655, 1657 (Fed. Cir. 1990). The law does not permit supplementing the disclosure of an allegedly anticipatory reference, nor permit mere speculation about what the reference *might* teach.

The pending rejection rests on speculative and uncertain results that fail to provide a legally sufficient basis for anticipation. The Table displays the results of application of selected references cited in Applicants' IDS to convert Neer to micrograms.

Reference	**IDS Reference Code**	**Specific Activity (units/ug)**	**Conversion of Neer's 100-700 units to microgram**
Finkelstein (1994)	CAH	12.5	8 ug - 56 ug
Fujita (1999)	CL	3.3	30 ug - 212 ug
Hodsman (1997)	CN	15	6.7 ug - 46.6 ug
Lane (1998)	CE	16	6.2 ug - 43.8 ug
Reeve (1980)	CO	7.5	13.3 ug - 93.3 ug
Reeve (1987)	CU	10	10 ug - 70 ug
Sone (1995)	CAA	3	33.3 ug - 233.3 ug

Clearly, the importation of specific activity values from the prior art to interpret Neer yields broadly divergent results that are anything but certain. The reason for this uncertainty is clear: the prior art provides specific activity values for hPTH(1-34) that are broadly dispersed from a low of 3 U/ug to a high of 16 U/ug (*cf.* Table).

The rejection fails to account for this uncertainty. However, it cannot be ignored without dismissing the rigorous standard required for anticipation. An allegedly anticipatory reference *must* teach *each element* of the claimed invention, either expressly or inherently. Anticipation cannot rest on mere speculation or guesswork about the teachings, or the possible interpretation, of a reference. It must rest on what is certain and necessarily taught by the reference.

Apparently the Examiner disagrees. The rejection asserts on Page 7 of Paper 14 that the published specific activity values of PTH(1-34) are "quite close to each other and quite consistent." As the Table clearly shows, however, the cited references demonstrate more than a five-fold variance from lowest to highest published specific activity values for PTH(1-34). The same degree of ambiguity and uncertainty is transferred to Neer upon conversion thereby undermining any argument as to what Neer *necessarily* teaches.

Applicants respectfully assert the rejection is uncertain, ambiguous, and wholly arbitrary. The Examiner chose two specific activity values from the prior art (i.e. 16 U/ug and 12.5 U/ug) that, when applied to Neer, generate ranges that overlap with Applicants' claimed 20 ug dose (i.e. 6-44 ug and 8-56 ug, respectively). No justification appears in the rejection for choosing *these* particular values as opposed to other values from the art. It cannot be argued that the choice of specific activity has no impact on the result. The choice of specific activity is highly relevant to the outcome. For example, applying Sone's specific activity (3 U/µg; IDS reference CAA), yields a range of 33.3 - 233.3 µg for Neer. Applying Fujita's specific activity (3.3 U/ug; IDS reference CL) yields a range of 30 - 212 ug for Neer. With these calculations, Applicants' claimed dose of 20 µg/day clearly falls outside the scope of Neer.

Clearly, the basis for the rejection is arbitrary. The results obtained are uncertain and contrary to the explicit requirement for certainty in an anticipatory reference.

The rejection has not established a *prima facie* case of anticipation and has failed to show that *Neer* necessarily discloses Applicants' claimed 20 microgram dose. Arbitrary selection of a specific activity value from sources outside Neer is improper to establish anticipation. Applicants respectfully request withdrawal of the rejection.

Conclusion

Neer provides no basis to convert the disclosed "units" dosage to micrograms, and no basis for comparison with Applicants' claimed invention. The permissible use of more than one reference to show anticipation is limited to the narrow purpose of "explaining" what is contained in the primary reference, not adding information that is not already there.

The present rejection imported specific activity values into Neer from secondary prior art references that go beyond merely "explaining" what was contained in Neer. The rejection supplements Neer with critical information that is not contained in Neer. As such the rejection exceeds the permissible standard for relying on multiple references for an anticipation.

Furthermore, the rejection rests on uncertain results. An allegedly anticipatory reference *must* disclose the claimed invention with certainty; mere *possibility* fails to achieve this standard. The present rejection rests on speculation at best about what Neer possibly *could* teach, not on what Neer *unequivocally does* teach. Uncertainty about what Neer teaches undermines any basis for anticipation of Applicants' claimed invention.

Applicants submit that each point of the rejection has been adequately addressed and, in view of the amendment and remarks, respectfully request withdrawal of the rejection and passage of the application to issuance. Applicants respectfully request a personal interview prior to a first Office Action.

Respectfully submitted,

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